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REVIEW ARTICLE

Evolving concepts in the management of renal osteodystrophy

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Abstract

Renal osteodystrophy presents an ongoing challenge for clinicians, despite numerous therapeutic advances in its management. Hyperphosphatemia is found in approximately 70% of patients undergoing regular dialysis, and secondary hyperparathyroidism is common. Soft-tissue and vascular calcifications also often occur in patients with end-stage renal disease. Recently, concern has developed about potentially adverse consequences associated with certain therapeutic interventions designed to manage secondary hyperparathyroidism and renal bone disease, particularly with regard to vascular calcification. Treatment with vitamin D sterols and the use of large oral doses of calcium as a phosphorus-binding agent, either alone or together with vitamin D therapy increase the risk of soft-tissue calcification in patients with end-stage renal disease. Vascular calcification contributes substantially to the development of cardiovascular disease and to high mortality rates from cardiovascular causes. Therefore, it is appropriate to re-examine the guidelines for managing renal osteodystrophy in patients undergoing long-term dialysis. Alternative strategies for managing phosphorus retention are being implemented, and new phosphate-binding agents are being developed. Vitamin D analogs that may have a greater therapeutic index than calcitriol are also available for clinical use. The successful development of calcimimetic compounds would provide another mechanistically distinct therapeutic approach that could be used either alone or together with vitamin D to more effectively manage secondary hyperparathyroidism.

Key words: Calcium phosphates/blood, Kidney failure/chronic, Phosphorus, Vitamin D/adverse effects

中文摘要

雖然在醫療上已有極大進步，處理腎性骨營養不良在臨床醫學仍是一個難題。在定期接受透析者中，約有70%患有高磷酸鹽血症，而繼發性甲狀旁腺功能亢進亦很常見。晚期腎病患者中亦很常會出現軟組織及血管鈣化。近來越來越多人關注到，處理繼發性甲狀旁腺功能亢進及腎性骨疾病的某些治療方案可能帶來的不良後果，尤其血管鈣化。以維他命D固醇及大劑量口服鈣作為磷結合劑的治療，不論單用或聯用維他命D治療，都會增加晚期腎病患者軟組織鈣化的危險；而血管鈣化大大地增加了發生心血管疾病的危險，且與高心血管死亡率相關。因此，有必要重新評估處理正接受長期透析患者腎性骨營養不良的指引。其他治療磷瀦留的替代策略已有施行，而新的磷結合劑亦正在發展中。現時亦已有可能比骨化三醇更具療效的類維他命D供臨床使用。仿鈣化合物的成功研製，能提供一種不同機制的治療方案；其單用或與維他命D聯用，或能更有效處理繼發性甲狀旁腺功能亢進。

INTRODUCTION

In its broadest definition, renal osteodystrophy encompasses all the disorders of bone and mineral metabolism that occur in patients with chronic renal disease (1). Despite numerous therapeutic advances, the

management of renal osteodystrophy presents an ongoing challenge for clinicians. Hyperphosphatemia is found in approximately 70% of patients undergoing regular dialysis, and secondary hyperparathyroidism is common (2). Soft-tissue and vascular calcifications also occur

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quite often in patients with end-stage renal disease. Therefore, the available strategies to manage these problems have been only partially successful.

In recent years, concern has developed about potentially adverse consequences associated with certain therapeutic interventions designed to manage secondary hyperparathyroidism and renal bone disease, particularly with regard to vascular calcification. Treatment with vitamin D sterols can increase serum calcium and phosphorus levels, and has been shown to increase the risk of soft-tissue calcification in patients with end-stage renal disease (3). The use of large oral doses of calcium as a phosphorus-binding agent, either alone or together with vitamin D therapy, may further increase this risk (4,5). Evidence has accumulated to suggest that vascular calcification contributes substantially to the development of cardiovascular disease and to high mortality rates from cardiovascular causes in the end-stage renal disease population (6,7). These considerations suggest that it is appropriate to re-examine the guidelines for managing renal osteodystrophy in patients undergoing long-term dialysis with the objective of maximizing the benefit and minimizing the risk.

MAJOR COMPONENTS OF CLINICAL MANAGEMENT

Hypocalcemia, hyperphosphatemia, and impaired renal 1,25-dihydroxyvitamin D synthesis each contribute to excess parathyroid hormone (PTH) secretion in patients with chronic renal failure (8,9). These disturbances are the target for therapeutic interventions aimed at preventing the development and controlling the progression of secondary hyperparathyroidism.

Maintenance of serum calcium levels

Hypocalcemia stimulates PTH release directly by diminishing the level of activation of the calcium-sensing receptor (CaSR) in the membrane of parathyroid cells (10). Plasma PTH levels increase within minutes when blood ionized calcium levels decrease, and variations in CaSR activity are primarily responsible for the minute-to-minute control of PTH secretion *in vivo*. Low ambient extracellular calcium concentrations also enhance the rate of pre-pro-PTH gene transcription, ultimately making more hormone available for secretion; this response, however, requires many hours (11). Hypocalcemia that is sustained for days, weeks, or months leads to parathyroid gland hyperplasia, a prominent feature of secondary hyperparathyroidism caused by chronic renal failure that further contributes to excess PTH secretion (12). Recent observations suggest that signaling via the CaSR is an essential mediator of this response (13). Hypocalcemia must be avoided, therefore, to prevent the

development of overt secondary hyperparathyroidism in chronic renal failure.

In the past, hypocalcemia was a common biochemical finding in patients with advanced renal insufficiency and in those starting dialysis. Two factors largely accounted for this change (14). First, the calcium content of most renal diets that are designed to limit phosphorus intake is less than that required for adequate calcium nutrition. Second, intestinal calcium absorption is suboptimal in many patients with renal failure because renal calcitriol synthesis is impaired (15). Both disturbances can aggravate secondary hyperparathyroidism if corrective measures such as dietary calcium supplementation or treatment with calcitriol are not implemented. This was often the case during the 1970s and early 1980s when aluminum-containing compounds were widely used as phosphate-binding agents, and before calcitriol became available for clinical use (16).

Because the long-term use of aluminum-containing medications has numerous adverse consequences, most patients with end-stage renal disease now use calcium-containing compounds to manage phosphate retention. The amounts required, however, exceed the 1500 mg of elemental calcium recommended by the World Health Organization to prevent age-related bone loss in the general population. Indeed, total calcium intake can approach 3 to 5 g per day, a portion of which is absorbed from the gastrointestinal tract via passive, vitamin D-independent mechanisms (17). In the absence of significant residual renal function, total body calcium balance can become quite positive, and several reports have documented that serum calcium concentrations decrease substantially when calcium-containing, phosphate-binding medications are discontinued abruptly in patients with end-stage renal disease (18-20). Such findings provide evidence that some of the calcium ingested as phosphate-binding medications enters the extracellular fluid and contributes to the development of hypercalcemia in as many as 40% of dialysis patients who use calcium-containing compounds as the primary method to manage phosphate retention (21,22). The concurrent administration of calcitriol or other vitamin D analogs further increases this risk (23).

In addition, several groups of investigators have noted that the likelihood of vascular calcification is greater in dialysis patients who ingest relatively large doses of calcium-containing, phosphate-binding agents (4,5). Vascular calcification reduces arterial wall compliance with adverse hemodynamic consequences. It may also contribute to the rupture of atherosclerotic plaques with subsequent arterial thrombosis (24). Because of these

concerns and because current therapeutic approaches may contribute inadvertently to excess cardiovascular morbidity and mortality in patients undergoing long-term dialysis, alternative methods for managing phosphate retention and hyperphosphatemia deserve careful consideration.

In this context, the use of supraphysiological doses of oral calcium as a method to control phosphate retention may not be advisable for patients with end-stage renal disease. One prudent alternative is to limit total daily calcium intake to a level sufficient to satisfy nutritional requirements but low enough to prevent total body calcium balance from becoming markedly positive. Unfortunately, only limited information is available to guide the formulation of definitive recommendations. Modest dietary calcium supplementation is probably required to maintain net intestinal calcium transport via passive mechanisms and to offset defects in vitamin D-dependent intestinal calcium transport in patients with advanced renal failure. A daily calcium intake in the range of 1500 to 2000 mg including dietary sources and amounts prescribed as oral calcium supplements should satisfy this objective in most patients with end-stage renal disease without producing overt calcium retention.

For patients with marked hyperphosphatemia where modest doses of calcium are inadequate to control serum phosphorus levels, aluminum hydroxide can be used for periods limited to a few weeks with little risk of aluminum retention or aluminum toxicity. This approach may also be suitable for patients with hypercalcemia, which precludes upward adjustments to prescribed doses of calcium-containing, phosphate-binding agents. Care must be taken, however, to avoid the concurrent administration of compounds such as citrate that can promote intestinal aluminum absorption.

As a potentially safer alternative, sevelamer, or polyallylamine hydrochloride, can be given either alone or together with modest oral doses of calcium to diminish intestinal phosphorus absorption and to manage phosphate retention. Wide-ranging adjustments to the dose of sevelamer can be made as tolerated to normalize serum phosphorus levels without inducing episodes of hypercalcemia. Because sevelamer contains no calcium, patients with end-stage renal disease who use this agent exclusively to manage phosphate retention may not ingest adequate amounts of calcium each day as discussed previously. It will be necessary, therefore, to provide moderate supplemental oral doses of calcium to avoid dietary calcium deprivation in many patients who are treated with sevelamer, but there is little information that directly addresses this issue.

Sevelamer also lowers serum total and low density lymphocyte cholesterol levels (25). This ancillary effect of treatment may ultimately prove to be beneficial for patients known to be at risk for developing cardiovascular disease. Long-term clinical experience with sevelamer is limited, and ongoing assessments are needed to confirm its safety and efficacy with continued use.

Compounds that do not contain either calcium or aluminum offer alternative approaches to managing phosphate retention, but none are currently available for clinical use (26,27). Lanthanum carbonate is an effective phosphate-binding agent in experimental animals, and clinical trials to assess its safety and efficacy in patients with end-stage renal disease are ongoing (27). Preparations such as iron citrate, iron chloride, and iron ammonium citrate have also been evaluated as phosphate-binding agents (26). The value of these and other compounds for clinical use will ultimately depend on their efficacy in controlling serum phosphorus levels, the ability of patients to consume the large amounts usually required, the absence of untoward side effects, and the lack of toxicity with long-term treatment.

Control of serum phosphorus levels

Hyperphosphatemia promotes the development of parathyroid gland hyperplasia, but the mechanisms responsible have yet to be clarified. High ambient phosphorus levels also affect post-transcriptional events that enhance messenger ribonucleic acid translation and PTH synthesis (28-31). In the clinical setting, persistent hyperphosphatemia seems to attenuate the effectiveness of calcitriol therapy to lower serum PTH levels in patients with established secondary hyperparathyroidism. Thus, adequate control of serum phosphorus levels is critical to successful patient management.

Until recently, most published guidelines for the management of phosphate retention in patients with end-stage renal disease recommended that serum phosphorus levels be maintained at values modestly above the upper limit of normal. This advice was based, in part, on reports from the older literature indicating that osteomalacia can occur in hemodialysis patients who develop persistent hypophosphatemia during treatment with aluminum hydroxide (32). Adequate skeletal mineralization does not occur when serum phosphorus levels are subnormal. Maintaining serum phosphorus levels above the upper limit of normal was thought to diminish the risk of osteomalacia in patients with chronic renal failure.

Despite such theoretical considerations, guidelines about the optimal range for serum phosphorus concentrations in patients with end-stage renal disease are being re-

examined because of several recent observations. Hyperphosphatemia has been shown to be an independent risk factor for death in patients undergoing hemodialysis even after adjusting for established cardiovascular risks and other comorbid conditions (2). Death from cardiovascular causes largely accounts for excess mortality in such patients (7). In a recent study that documented the presence of coronary artery calcification in young adult patients undergoing dialysis, serum phosphorus levels tended to be higher and the calcium-phosphorus ion product in serum was greater in patients with evidence of coronary calcification than in those without this abnormality (4). Such findings suggest that the adverse consequences of phosphate retention in patients treated with dialysis include an increased risk for cardiovascular disease.

Additional studies are needed to determine the relationship between disturbances in mineral metabolism and the development of vascular calcification and adverse cardiovascular outcomes in patients with end-stage renal disease. It is possible that therapeutic interventions aimed at managing phosphate retention, such as the use of very large oral doses of calcium, either alone or in conjunction with vitamin D, rather than hyperphosphatemia *per se*, are primarily responsible. Evidence is accumulating, however, to suggest that abnormalities in mineral metabolism and/or the therapeutic interventions designed to manage them may inadvertently contribute to the development and progression of vascular disease in patients undergoing long-term dialysis.

In this regard, alternative dialysis regimens, such as daily nocturnal hemodialysis and short-duration hemodialysis that is done 6 days per week, provide strikingly better control of serum phosphorus levels than conventional thrice-weekly hemodialysis (33). Such findings strongly suggest that current dialysis schedules are only marginally adequate for managing phosphorus retention in patients who have little or no residual renal function. In many cases, they are clearly inadequate. Although necessary and appropriate, efforts to maintain adequate protein nutrition with its obligatory phosphorus burden only further compromise the ability of patients to achieve net neutral total-body phosphorus balance during the course of the week. Effective control of phosphorus retention in patients with end-stage renal disease may thus require a radical departure from traditional approaches to dialysis management.

Control of excess parathyroid hormone secretion

Until the late 1980s, the active treatment of secondary hyperparathyroidism in patients undergoing regular

hemodialysis entailed the use of daily oral doses of vitamin D sterols. Calcitriol, or 1,25-dihydroxyvitamin D₃, was used predominantly in the United States (US), whereas alphacalcidol, or 1-alpha-hydroxyvitamin D₃, was available in Europe (23,34,35). Parenteral preparations of each agent subsequently became available, and most hemodialysis patients in the US are now managed using thrice-weekly intravenous doses of calcitriol or other vitamin D analogs. This approach assures patient compliance, allows larger cumulative doses of vitamin D to be given each week, and produces very high concentrations of calcitriol in serum shortly after intravenous administration. Although pharmacokinetic considerations suggest that intermittent parenteral therapy should be more effective than treatment with daily oral doses of calcitriol for controlling excess PTH secretion and reducing plasma PTH levels, recent clinical studies have failed to demonstrate substantive differences between these two therapeutic approaches (36,37). The frequency of episodes of hypercalcemia and/or hyperphosphatemia also does not differ between treatment regimens.

Because serum calcium and phosphorus levels often increase during treatment with calcitriol, other vitamin D analogs have been developed in an effort to reduce these two dose-limiting side effects of vitamin D therapy and to lower the risk of soft-tissue and vascular calcification (23). Two compounds currently available for clinical use in the US are 19-nor-1,25-dihydroxyvitamin D₂, or paricalcitol, and 1-alpha-hydroxyvitamin D₂, or doxercalciferol (38,39). Both are vitamin D₂ derivatives. A third vitamin D₃-derived compound, 22-oxacalcitriol or 22-oxa-1,25-dihydroxyvitamin D₃, is now available for clinical use in Japan.

All three compounds have been shown in clinical trials to lower serum or plasma PTH levels in patients with secondary hyperparathyroidism caused by end-stage renal disease. Indeed, plasma PTH levels decreased by an average of 25% to 30% during the first few weeks of treatment with either paricalcitol or doxercalciferol. It remains uncertain, however, whether the frequency of episodes of hypercalcemia and/or hyperphosphatemia is less during treatment with new vitamin D analogs than with calcitriol. Studies that compare directly the efficacy and frequency of side effects with each treatment have yet to be published. Nevertheless, the availability of new vitamin D analogs may ultimately provide a way of managing secondary hyperparathyroidism while diminishing the risk of soft-tissue and vascular calcification during vitamin D therapy.

Calcimimetic agents are small organic molecules that

activate the CaSR in the membrane of the parathyroid cell, thereby inhibiting PTH release. They represent a novel approach to managing excess PTH secretion because their mechanism of action differs fundamentally from that of the vitamin D sterols (40). The efficacy of calcimimetic agents in reducing plasma PTH levels has been documented in short-term studies of hemodialysis patients with secondary hyperparathyroidism, and long-term clinical trials in larger numbers of patients are currently underway (41).

In contrast to treatment with vitamin D, serum calcium concentrations decline modestly and serum phosphorus levels often decline during calcimimetic therapy in patients with secondary hyperparathyroidism (42,43). Thus, several biochemical abnormalities that have been associated with the development of soft-tissue and vascular calcification in patients with end-stage renal disease improve as plasma PTH levels decrease. Because their mechanisms of action differ, combined therapy with calcimimetic agents and vitamin D sterols may be a particularly effective approach to managing excess PTH secretion in patients with secondary hyperparathyroidism, particularly those with severe disease.

Activation of the CaSR has been reported to affect several fundamental cellular processes including proliferation, differentiation, and apoptosis (44-46). Apart from their effect to diminish PTH secretion, studies in rats with renal failure suggest that calcimimetic compounds impede the development of parathyroid gland hyperplasia (47). Moreover, signaling via the CaSR seems to be sufficient to prevent the development of parathyroid gland hyperplasia in mice with inactivating mutations in the gene encoding the vitamin D receptor when serum calcium levels are maintained within the normal range by dietary maneuvers (13,48). Calcium *per se*, acting through its receptor, may therefore have a fundamental role in modulating parathyroid gland hyperplasia in chronic renal failure.

CONCLUSIONS

The risks associated with persistent hyperphosphatemia and with the use of large doses of calcium and vitamin D to manage renal osteodystrophy in patients with end-stage renal disease are becoming more widely recognized. Alternative strategies for managing phosphorus retention are being implemented, and new phosphate-binding agents are being developed. Vitamin D analogs that may have a greater therapeutic index than calcitriol are also available for clinical use. The successful development of calcimimetic compounds would provide another mechanistically distinct therapeutic approach that could be used either alone or

together with vitamin D to more effectively manage secondary hyperparathyroidism.

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